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Separable systems for recovery of finger strength and control after stroke

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Abstract

Loss of hand function after stroke is a major cause of long-term disability. Hand function can be partitioned into power grip and finger individuation, with the former requiring high levels of force and the latter precise control of digits. Here we introduce an ergonomic device and a novel paradigm that allows the independent quantification of these two aspects of hand function. Using this task, we tracked over 50 patients with stroke-induced hemiparesis over the first year of their recovery. Most recovery of both strength and finger individuation occurred in the first month after stroke. Notably, at any time after stroke the two functional aspects were related by an invariant curvilinear recovery function: strength and control were correlated up to a threshold level of ~60% recovery in strength, after which further increases in strength did not lead to automatic increases in control. Patients also showed consistent recovery pattern above or below the main recovery function. The most parsimonious explanation of this finding is that there are two systems mediating recovery of hand function after stroke. One system, which determines the lower bound of the time-invariant function, contributes strength and a limited degree of finger control. The other system contributes additional control. We speculate that these two behaviorally identified systems are consistent with the known properties of the reticulospinal and corticospinal tracts. Indeed, lesion volume analysis indicated that the extent of lesions in cortical regions and descending pathways (cortical spinal tract) were more strongly correlated with the recovery of fine finger control than strength.

Keywords:

Finger individuation, strength, stroke, recovery, plasticity

Introduction

Power grip and fine control of individual finger movements are two complementary aspects of hand function. The most common observation after stroke is that both are impaired (Kamper and Rymer, 2001; Kamper et al., 2006; Lang and Schieber, 2003). Weakness presents as difficulties in voluntarily opening of the hand, extending the wrist and fingers against resistance, and producing a strong grip (Colebatch and Gandevia, 1989; Kamper et al., 2003; Raghavan et al., 2006; Trombly et al., 1986). Loss of fine finger control manifests as inability to move a single finger and keep the others immobile, or to move the fingers sequentially, both of which impair the ability to perform tasks such as typing or buttoning a shirt (Kamper and Rymer, 2001; Lang and Schieber, 2004; Li et al., 2003). When strength does recover after stroke, fine finger control often remains impaired, causing lasting disability (Heller et al., 1987; Sunderland et al., 1989). Animal and human studies suggest that fine control of the hand is mainly subserved by the corticospinal tract (CST) (Brinkman and Kuypers, 1973; Heffner and Masterton, 1975; Kuypers, 1982; Lang and Schieber, 2003; Lemon, 2008; Porter and Lemon, 1993), whereas full hand grip can also be generated by brainstem pathways (Lawrence and Kuypers, 1968a, 1968b), primarily the reticulospinal (RS) tract (Baker, 2011; Riddle et al., 2009). In the current study we sought to investigate the relationship between strength and control in hand over the time course of its recovery after stroke. We were specifically interested to test whether these two functional aspects recover in a lawful relationship together, or whether they recover independently.

One of the challenges in tracking the relationship between fine finger control and strength of the hand after stroke is the difficulty in disambiguating them with existing

Kommentiert [andreas.l1]: I think that we need to say something about the role of spasticity that develops with a delay and may add a third (negative) recovery system.

Kommentiert [JX2]: Spasticity is a separate issue from strength and control. It worth study on its own. However, here we didn't measure spasticity, and only focus on strength and control. To the degree control is affect by spasticity, the effect of it will be picked up by our measure.

We will mention in the discussion that spasticity-related deficit, such as difficulties in finger extension is not the focus of this study.

behavioral tasks. Hand function after stroke has traditionally been evaluated with tests such as the Fugl-Meyer Assessment (FMA) (Fugl-Meyer et al., 1975), the Nine-Hole Peg Task (9NPT) (Sharpless, 1982), and the Action Reach Arm Test (ARAT) (Lyden and Lau, 1991). These measures, however, are sensitive to both deficits in strength and fine finger control. We therefore needed to develop a task that could isolate these two aspects of hand function by removing any obligatory relationship between them, i.e. that our control measure would not be dependent on strength (Reinkensmeyer et al., 1992), Schieber and colleagues (1991) devised an individuation task that requires participants to move individual fingers while keeping the non-moving digits stationary. Movements of the passive fingers were used as a measure of loss of fine control. Involuntary enslaving of passive fingers can also be observed during isometric force production tasks in healthy controls, and such enslaving increases as a greater level of force is applied by the active finger (Li et al., 1998). Here we designed an ergonomic keyboard that continuously records the forces produced by all ten digits. We first measured the maximal voluntary force (MVC) that a participant could produce with each finger. To disambiguate fine finger control from strength, we quantified the relationship between enslaving of the passive fingers and the force produced by the active finger by varying target force levels between 20 – 80% of MVC. The slope of this relationship provides a measure of fine finger control that is independent of individual differences in strength. So for example, a rock climber may have stronger fingers than a pianist but the slope of the relationship between enslaving and force will be independent of this absolute strength difference.

Our task enabled us to independently track hand strength and individuation in patients over a one-year period after stroke and determine the nature of the relationship

between these two measures as recovery evolves. One possibility is that these two aspects of hand function recover independently. For example, a patient may remain quite weak but have good recovery of individuation, or a patient may recover a lot of grip strength but fail to move any of the digits independently. Alternatively, recovery may be such that when strength recovers so does individuation because repair processes are proceeding to a similar degree in the neural substrates for these two independent aspects of hand function.

Methods

Participants

Fifty-four first-time ischemic stroke patients with hemiparesis (34 male, 20 female; mean age 57.4±14.9 years) were recruited from three centers: Johns Hopkins Hospital, Columbia University, and University Hospital of Zurich. According to Edinburgh Handedness Inventory (Oldfield, 1971), 44 patients were right-handed, and 10 were left-handed. All patients met the following inclusion criteria: 1) First-ever clinical ischemic stroke with positive DWI lesion within the previous 2 weeks; 2) Residual one-side upper extremity weakness (MRC < 5); 3) Ability to give informed consent and understand the tasks involved. We excluded patients with one or more of the following criteria: initial UE FMA > 63/66, under 21 years, hemorrhagic stroke, space-occupying hemorrhagic transformation, bihemispheric stroke, traumatic brain injury, encephalopathy due to major non-stroke medical illness, global inattention, large visual field cut (greater than quadrantanopia), receptive aphasia (inability to follow 3-step command), inability to give informed consent, major neurological or psychiatric illness

that could confound performance/recovery, or physical or other neurological condition that interferes with arm, wrist, or hand function recovery. Due to the exclusion of aphasic patients, the sample had a bias towards right-sided infarcts (17 left-sided, 37 right-sided). Detailed patient characteristics are listed in Supplementary Information Table S1, and lesion distribution is shown in Fig. 6A.

A total of 14 age- and education- matched healthy control participants (10 male, 4 female; mean age 64±8.2 years; 13 right-handed, 1 bi-dexterous) were also recruited at the three centers. The exclusion criteria for healthy controls were any neurological disorder or physical deficit involving the upper limbs.

All participants signed a written consent form that was approved by the local institutional human research review board at each study center. All procedures were approved by Institutional Research Board at each study center.

Clinical assessments

At each of the five visits, all participants were scored on several clinical outcome measures. Here we report data for the ARAT and FMA. Hand strength was also obtained for hand-grip (CITE JAMA), the first dorsal interosseous (FDI), and the flexor carpi radialis (FCR) using a hand-held dynamometer (Hoggan MiroFET2 Muscle Tester, Model 7477, Pro Med Products, Atlanta, GA).

Finger MVC and Individuation tasks

Patients were tested at the following 5 time points post-stroke: within the first 2 weeks (W1), at 4-6 weeks (W4), 12-14 weeks (W12), 24-26 weeks (W24), and 52-54 weeks (W52). Healthy controls were tested at comparable intervals.

At each visit, hand function was tested using an ergonomic device that measures isometric forces produced by each finger (Fig. 1A). The hand-shaped keyboard is comprised of 10 keys. Force transducers (FSG-15N1A, Honeywell®; dynamic range 0-25 N) underneath each key measured the force exerted by each finger with a sampling rate of 200 Hz. Real-time force traces for all ten digits were acquired using force transducers and National Instrument USB-621x devices interfacing with MATLAB (The MathWorks, Natick, MA) Data Acquisition Toolbox. Visual stimuli of the task were presented on the computer monitor, run by custom-written software using Psychotoolbox in MATLAB environment, run on a Windows machine.

Participants were seated in a comfortable chair, facing a computer monitor that presented the visual stimuli for the task. During the entire experiment, participants rested their two hands on the keyboards with each finger on top of a key, their wrists strapped and fixed on a wrist-rest, and their forearms extended and supported by foam arm rests. Throughout the experiment, ten vertical gray bars representing the 10 digits appeared on top of the screen, and another 10 vertical bars below them with equal length were used to present the amount of force to be exerted (Fig. 1B). Participants could monitor the force exerted by all 10 digits in real time by the heights of 10 small white lines moving along the force bars.

Two separate aspects of finger function were tested: maximal voluntary contraction (MVC) and individuation. During each MVC trial, the participant was asked

158 to depress one finger at a time with its maximum strength, and maintain the force level
159 for 2 seconds. The participant could press the other fingers as much as they wanted as
160 long as maximal force on the instructed finger was achieved. To signal the start, one
161 force bar corresponding to the instructed finger turn to green, and the participant was
162 instructed to bring the white line corresponding to the active finger to the highest possible
163 level by pressing that finger as hard as they could. MVC was measured twice per digit.
164 In the individuation task, participants were to depress each individual finger at a
165 sub-MVC level of force, while at the same time keeping their other fingers immobile on
166 the keys. Four target force levels were tested for each digit: 20%, 40%, 60%, and 80% of
167 MVC, and each level was repeated 4 times. On each trial, a section of a force bar turned
168 to green, with the height of the middle black line representing the target force level and
169 the green region around the middle line representing the 25% upper and lower bounds
170 around the force level (Fig. 1B). The participant was asked to bring the corresponding
171 white line up to the force target line, and maintain the force level for 0.5 sec. If no
172 response passing the force threshold of 2.5 N was detected in 2 seconds, the trial was
173 terminated.
174 ----------
175 Insert Figure 1
176 ----------
177
178 ***Data analysis***
179 *Strength Index*. The 95th percentile of the force traces produced on each of the
180 two MVC trials was calculated as a measure of the MVC on each digit. We then averaged

these values across the two trials. A total of 6.67% of MVC trials were dropped because the force achieved on one of these trials was below 60% of the level produced by the same digit on the other trial. For these cases, the trial with the larger force as MVC measure was used. The overall strength of the hand was then calculated by averaging across 5 fingers. To quantify the impairment of the paretic hand we needed to account for the large inter-subject variability in overall strength. MVC of the non-paretic hand at W52 was used as the best estimate for the pre-morbid level of hand strength in each patient. If missing, it was estimated using a mixed-effects model (see below). All MVC values were then divided by this value, providing a Strength Index, with a value close to 1 implying full recovery. For control participants, one of the hands was assigned to take the role as the "non-paretic" hand for the purposes of normalization. To account for possible laterality effects, the assignment was performed such that the ratio of dominant to non-dominant hands (10:4) was similar to those found in the patients (37:17).

Kommentiert [andreas.l3]: Why are we using week 52 here. Are we not expecting alterations in non-paretic hand strength to occur after the stroke (e.g. due to overuse)? How is premorbid dominance accounted for?

Kommentiert [JX4]: There does not seem to be much evidence of the change in strength due to overuse. Figure 2 shows that the overall non-paretic hand strength remained to be the same level after W4, and was comparable to healthy controls.

Individuation Index. A person's ability to control their fingers individually was quantified with an Individuation Index. If individuation ability is perfect, a participant should be able to press the instructed finger without any force being exerted by the passive fingers. For each time bin t (5ms) in a single trial, we calculated the deviation of the force of the passive fingers ($F_{t,j}$) from the baseline force (BF_j), which was assessed at the beginning of the trial when a go cue was presented. This deviation was averaged over all bins (T) in the force trace from the go cue to the end of the trial:

$$meanDevP = \frac{1}{T}\sum_{t=0}^{T}\sqrt{\sum_{j=passive}(F_{t,j} - BF_j)^2} \quad (1)$$

where the index j denotes the jth passive finger. A higher *meanDevP* indicates more enslaving of the passive fingers.

For a measure of individuation ability, however, it is necessary to account for the relationship between *meanDevP* and the force produced by the active finger. As previously reported (Li et al., 1998) and as we observed, enslaving of passive fingers increases with higher active force (Fig. 1E). Furthermore, the relationship between the two variables was close to linear. Thus a good measure of individuation that is independent of strength is the amount of increase in *meanDevP* per N active force (i.e. the ratio of these two variables). This ratio can be estimated reliably by fitting a regression line without an intercept (i.e. the line needed to cross through the origin of the coordinate system). To reduce the influence of outliers, we used robust regression (Holland and Welsch, 1977), as implemented in the MATLAB (The MathWorks, Natick, MA) function robustfit. The slope of the regression line reflects individuation ability: The smaller the slope, the better the individuation ability, with the best case being 0, which means keeping the passive fingers perfectly immobile at any active force level. Because the regression slope is bounded by zero (as *meanDevP* is positive), its distribution is positively skewed. To allow for the use of parametric statistics we used the log-transform of the slope. We also inverted the sign of this value, so that higher values would correspond to better function. The log of the slope was calculated separately for each active finger and then averaged across fingers, giving the Individuation Index for the hand.

Measuring Reliability of the Strength and Individuation Indices. To determine the reliability of, the Strength and Individuation Indices, split-half reliabilities for both these measures were calculated. For the Strength Index, the two MVC trials for each digit were used in the two halves of the split. In each split, the Strength Index was determined by

averaging finger MVC's for the whole hand, and then normalized by the W52 MVC of the non-paretic hand within the same patient. The correlation was then taken between the two halves across all available sessions and patients.

For the Individuation Index, data from each finger was split such that two trials per force level were assigned to each split. The slope of the regression line and Individuation Index was then calculated separately for each split. We repeated the split multiple times, each time assigning trials at random and then averaged the split-half correlations from all splits for more reliable results.

Split-half correlation will underestimate reliability because the variability in each half will be higher than the overall variability in the data (Guttman, 1945). The estimate was therefore corrected using the formula

$$r_{full} = \frac{2r_p}{r_p + 1} \quad (2)$$

where r_p is the correlation between the two splits.

Noise ceiling for correlations. One measure of particular interest in this study was the correlation *between* the strength and individuation indices at a given time point, and the correlation *within* each measure across time points (stability). The correlation between two measures, either cross-sectionally or longitudinally, will be smaller than 1 even if the two variables are perfectly related. This is because both measures contain some measurement noise. Based on the full reliability, the noise ceiling for the correlation of two component variables can be estimated, that is how much two noisy variables should correlate with each other if they were perfectly related (eq. 2):

$$r_{noise\ ceiling} = \sqrt{r1_{full} * r2_{full}} \ . \quad (3)$$

Statistical analysis. Data analysis was performed using custom-written MATLAB (The MathWorks, Natick, MA) and R (R Core Team, 2012) routines. The analysis focused on measures for two aspects of hand function: MVC and Individuation Index, but also on standard clinical assessment, such as Fugl-Meyer scores, ARAT, and Dynamometry strength measures (See Supplemental Materials).

Given that we had many missing values (only 15 patients completed all 5 time points; on average each patient completed 3.3 sessions), we used linear mixed-effect models implemented in the *lme4* package in R (Bates et al., 2014) to analyze the changes in these measures over time. Participant was taken as a random factor. Time point (five time points from W1-W52) and hand condition (paretic, non-paretic, and control) were considered fixed factors. Mixed-effect model estimation was implemented using restricted maximum likelihood method (Laird and Ware, 1982).

To test the hypothesis of time-invariant function between strength and individuation, a two-segment piecewise linear function was fitted. This function had four free parameters: the intercept, the location of the inflection point, and the slope on each side of the inflection point (see details in Supplemental Materials). The maximum-likelihood (or least-squares) estimates of these parameters were obtained by using the non-linear optimization routine fminsearch in Matlab. Leave-one-out cross-validation (Picard and Cook, 1984) was used to evaluate whether this function changed systematically over time, or whether it was time-invariant. The time-invariant model with fixed parameters across all time points was compared with a more complex model that allowed free parameters for each time point. Cross validation provides an unbiased

estimate of a model's ability to predict new data and automatically penalizes models that are too complex.

Severity stratification. After group-level analysis, patients were further divided into severe and mild groups, to examine what determines good recovery of hand function. The division was determined by whether the final Strength Index fell above or below the inflection point (0.59, see above). An alternative splitting method that would not bias the results to either Strength or Individuation was also used. In this approach, the first principle component in the 2D space defined by the final scores (mean of W24-52) for Individuation Index against Strength Index was used as a combined impairment measure, and then the groups were split by a cutoff point that maximized the between-group separation. Accidentally, these two approaches ended up with the same partitions.

Lesion analysis. Each patient's lesion was quantified as percentage volume affected by stroke in eight ROI's based on diffusion tensor images (DTI) and diffusion weighted images (DWI) (see details in Supplemental Materials). The averaged lesion distribution map across the entire patient sample in the current study is shown in Fig. 5A. Here we focus on the difference between cortical gray matter vs. sub-cortical white matter along the corticospinal tract (CST) extracted from four ROIs: 1) pre-central gyrus, 2) superior corona radiata, 3) posterior limb of internal capsule, and 4) cerebral peduncle. These percentage volume affected values were then correlated with our main outcome measures, Strength and Individuation Indices.

Results

A total of 54 acute stroke patients and 14 healthy controls underwent five test sessions over a one year period: 1-2 weeks (W1), 4-6 weeks (W4), 12-14 weeks (W12), 24-26 weeks (W24), and 52-54 weeks (W52) after the stroke. Data included in the final analysis were a total of 242 sessions tested in 53 patients (one patient dropped out before the completion of their first session) and 14 controls. Forty-one patients and twelve controls completed >= 3 sessions. Non-tested sessions were treated as missing data and all available data were used in the statistical analysis (see Methods).

Strength and individuation indices had good reliability

When introducing a new instrument it is important to first establish its reliability, i.e., how accurately can the difference between subjects and changes within subject be determined. To compute reliability, data from each testing session were split in half. Strength and Individuation Indices were calculated for each half, and correlation between the measures from the two halves were determined for the paretic hand across all patients and weeks. The reliabilities of the measures on the whole data set were then estimated by correcting for underestimation inherent in split-half method (see Methods, eq. 2).

MVC for healthy controls had an average value of 21.04 N (SD = 8.34) for the dominant hand, and 22.41 N (SD = 7.18) for the non-dominant hand. The normalized Strength Index (see Methods) for the controls' dominant hand was 0.98 (SD = 0.19), and non-dominant hand was 1.09 (SD = 0.27). For patients, the mean for non-paretic hand was 0.92 (SD = 0.20), and for the paretic hand it was 0.56 (SD = 0.37). The adjusted split-half reliability across all patients and weeks for the Strength Index was r_{full} = 0.99, which indicates excellent reliability.

Kommentiert [andreas.l5]: Unexpected that the dominant hand is weaker…

Kommentiert [JX6]: Yes, it's an interesting finding. In fact, the hand grip, FDI and FCR strength as measures by Dynamometry were consistent with those in the literature that dominant hand was stronger than the non-dominant hand. But our MVC measures showed the opposite, and it seem to be mainly driven by the index finger.

316 The Individuation Index captured the relationship between the force exerted with
317 the active finger and the amount of involuntary force changes (enslaving) in the passive
318 fingers. Lower values indicate more impaired individuation. Healthy, age-matched
319 controls showed, on average, an Individuation Index of 2.82 (SD = 0.56). This refers to a
320 slope of 0.069 (SD = 0.037), meaning that for a finger press of 10N the mean deviation of
321 the passive fingers was 0.69N. Consistent with our effort to construct an individuation
322 measure that is independent of strength, the overall correlation between Individuation and
323 Strength Indices in controls was very low in the dominant hand $r = -0.06$, $p = 0.64$, and
324 that in the patients' non-paretic hand was $r = 0.07$, $p = 0.34$. However, for the controls'
325 non-dominant hand, there was a slight negative correlation between Strength and
326 Individuation Indices ($r = -0.33$, $p = 0.01$). The adjusted split-half reliability of the
327 Individuation Index for the paretic hand of all patients was $r_{full} = 0.99$.
328
329 ***Correlation with standard clinical measures***
330 The Strength and Individuation Indices were compared with existing clinical
331 measures: the Fugl-Meyer (a measure of impairment) and ARAT (a measure of activity)
332 Table 1 shows the correlations for all four measures obtained from the paretic hand
333 across all time points. Overall, all correlations were very high ($p = 1.69\times10^{-31}$), indicating
334 that all the measures could detect severity of the hand function deficit. The correlation
335 between the two clinical measures was 0.91, whereas the correlation between Strength
336 and Individuation Index was 0.73, a significant difference ($z = 5.47$, $p = 6.0\times10^{-8}$, using z-
337 test with N = 164, Fisher, 1921). Given comparable reliabilities for all measures this
338 difference unlikely results from measurement noise – rather it suggests that our Strength

and Individuation Indices measure two different aspects of the hand function, whereas the clinical scales tend to capture a mixture of strength and control.

Insert Table 1

Most recovery of both strength and control occurred in the first 3 months after stroke

We first examined the time courses of recovery for strength and control for the paretic hand. For both measures, most of the recovery appeared to occur within the first 12 weeks after the stroke (Fig. 2A,B). To evaluate this statistically, we applied a model with a fixed effect of Week and a random effect of Subject and tested the effect of week by using a likelihood ratio test against the null model with random effect only. Results indicate that both Strength and Individuation Indices significantly improved over time (Strength: $\chi^2 = 47.57$, $p = 5.32\times10^{-12}$; Individuation: $\chi^2 = 14.79$, $p = 0.0001$). Paired *t*-tests between adjacent time points showed significant improvement of the Strength Index up to week 24 (W1-4: $t(27) = 3.53$, $p = 0.0015$; W4-12: $t(34) = 3.33$, $p = 0.002$; W12-24: $t(32) = 2.40$, $p = 0.02$; W24-52: $t(27) = 1.39$, $p = 0.17$). The Individuation Index showed a significant improvement between week 4-12 (W1-4: $t(27) = 0.95$, $p = 0.35$; W4-12: $t(34) = 3.01$, $p = 0.0048$; W12-24: $t(32) = 1.50$, $p = 0.14$; W24-52: $t(27) = -0.40$, $p = 0.69$). A direct comparison between the rate of change in *z*-normalized scores of the two variables for the time period W1-4 vs. W4-12 using a MANOVA yielded a significant effect (Wilks' $\lambda = 0.85$, $p = 0.02$) (Fig. 2C). Thus, despite overall similarity, there was a

small but significant difference in the time course of recovery of strength and strength-independent control, with strength showing faster early recovery.

That most change in both strength and control occurred over the first 12 weeks is also apparent in the correlations for each variable calculated at adjacent testing time points across individuals (Fig. 2D). The correlations between weeks 1 and 4, and between weeks 4 and 12 for both measures were significantly lower than those for subsequent time points, (Strength Index: $z = -2.29$, $p = 0.022$, Individuation Index: $z = -3.81$, $p = 0.00014$, using z-test with N = 28 (Fisher, 1921)). Thus, the relative position of the patients with respect to the mean recovery curve changed more during the first 12 weeks across the first three testing sessions than in the 6 months between the last two sessions. This correlation difference cannot be attributed to measurement noise, as both measures had stable reliabilities at all time points (dashed line, Methods). Thus, the lack of stability of these measures during early recovery reveals some meaningful biological change in the motor system.

Insert Figure 2

The non-paretic hand also showed mild weakness in the first month after stroke. Likelihood ratio test of the random-effect model showed a significant effect of Week for Strength Index ($\chi^2 = 8.77$, $p = 0.003$, Fig. 2A). In contrast, the change in Individuation Index across different time points was not significant ($\chi^2 = 3.14$, $p = 0.076$, Fig. 2B). The increase in Strength Index is unlikely to be related to a general practice effect, as for healthy controls, MVC slightly decreased over time, albeit not significant ($\chi^2 = 2.89$, $p =$

384 0.088), which might be due to reduced effort. The Individuation Index maintained at a
385 similar level over the whole year ($\chi^2 = 0.38$, $p = 0.54$).
386 In summary, inspection of the time course of recovery revealed fast early changes
387 after the stroke, with stabilization of recovery around 3-6 month. We also found that
388 strength recovered more in the first month than did the Individuation Index.
389
390 ***A time-invariant function relates strength and strength-independent control***
391 The small differences in time courses for strength and control recovery suggested
392 that there might be two (partly) independent mechanisms at work. To further examine the
393 relationship between strength and individuation, we plotted the two variables against each
394 other for each testing time-point (Fig. 3A). For lower levels of strength, there seems to
395 be a clear correlation between strength and individuation; whereas above a certain
396 strength level the Individuation Index seems to reach ceiling, resulting in a distinct
397 curvilinear shape for the overall relationship. Although patients tended to move from the
398 lower left corner of the plot to the upper right corner over the time course of recovery, the
399 overall shape of the strength-individuation relationship seemed to be remarkably
400 preserved across weeks.
401 To test this observation formally, we first found a good functional form to
402 describe the strength-individuation relationship. We used data from all time points and
403 evaluated the fit of a *piecewise function* with two linear segments connected at an
404 inflection point using leave-one-out crossvalidation. This functional form gave us a good
405 fit to the data (leave-one-out cross-validated $R^2 = 0.58$, Fig. 3B). We also explored *first-*

406 *fourth order polynomial* functions, which all resulted in worse fit (cross-validated R^2 <
407 0.53).

408 We then tested whether the relationship between strength and control changed
409 across weeks. Again, using leave-one-out cross-validation, the time-invariant model with
410 fixed parameters across all weeks was compared with a model that allowed free
411 parameters for each week (time-varying model). Because of the use of cross-validation,
412 the more complex model does not automatically provide better R^2 values – rather, cross-
413 validation automatically penalizes models that are too complex. The overall cross-
414 validated R^2 for the time-varying two-segment piecewise linear function was 0.50, as
415 compared to $R^2 = 0.58$ for the time-invariant model.

416 These results suggest that there is a time-invariant recovery relationship between
417 strength and strength-independent control after stroke, which consists of two phases: up
418 to a certain level of strength (59.2% of non-paretic hand), Strength and Individuation
419 Indices are strongly correlated ($r = 0.75$, $p = 9.97\times10^{-18}$); after strength exceeds this
420 threshold, the two variables are not correlated any more ($r = 5.13\times10^{-4}$, $p = 0.996$).

421 ----------

422 Insert Figure 3

423 ----------

424 A possible reason for the lack of correlation in the second phase is a ceiling effect
425 for the Individuation Index. To check for this possibility, we split the patients into a
426 group with good (N = 24) vs. poor (N = 13) recovery (see Methods). Although the
427 patients' with good recovery showed a Strength Index that approached the level of the
428 controls (Fig. 4A), the mean Individuation Index never fully recovered (Fig. 4B). This

observation was confirmed by independent samples *t*-tests showing the *mean* (W24, 52) Individuation Index for patients with good recovery was significantly impaired relative to controls ($t(36) = -2.06$, $p = 0.046$). The same *t*-test for the Strength Index was not significant ($t(36) = -1.71$, $p = 0.098$). Thus the lack of correlation between strength and control for a strength index > 60% cannot be attributed to a ceiling effect.

Insert Figure 4

These results suggest that recovery of both strength and control can be captured as traversal along a time-invariant function relating the two. Differences in recovery arise because patients vary substantially in the distance they move along this function: some initially severely impaired patients make good recovery, moving past the inflection point of 60% strength (exemplified by the yellow dot in Fig. 3A). Other severely impaired patients fail to reach the inflection point (red dot in Fig. 3A). Finally, some mildly impaired patients start off beyond the inflection point and show a range of control capacity.

An additional recovery component for control combines with the time-invariant recovery function.

The fact that recovery of both strength and strength-independent control can be captured by a single time-invariant function suggests that a single underlying process drives recovery of both aspects of hand function. It, however, is possible that there is an additional recovery process that determines whether any given patient lies above or

below the mean function. If such an additional process exists, a given patient should occupy a consistent position above or below the recovery function.

To test for this possibility we investigated the residuals of the Individuation Index for each patient and each time point after subtracting out the mean two-segment piecewise linear recovery function. If the variability above and below this mean function was purely due to noise, we should observe no consistent correlation between residuals for each patient from week to week. Alternatively, if the residuals were correlated across weeks, it would indicate that some patients were consistently better at individuation than that predicted from the function, and others were consistently worse – suggesting an additional factor mediating individuation recovery (green arrow in Fig. 6A).

Correlations of residuals from adjacent time points across patients were initially quite low (W1-4: $r = 0.21$, $p = 0.29$). However, from week 4 onwards, most patients' distances from the mean function remained stable (Fig. 3C, W4-12: $r = 0.56$, $p = 0.0005$; W12-24: $r = 0.70$, $p = 5.15\times10^{-6}$; W24-52: $r = 0.73$, $p = 0.00001$) (Fig. 3D). This consistent structure in residuals is the evidence for an extra factor contributing to individuation ability after stroke recovery. The fact that the week-by-week correlation of the residuals was low for initial time points indicates that this factor does not just represent differences in pre-morbid ability to individuate, nor the amount of sparing in a particular neural system after the stroke. Rather, the increase in this correlation at later time points indicates an additional recovery process operating over and above the mean time-invariant strength-individuation function, and that this process is most active in the first month after stroke. As pointed out earlier, the low correlation between early time points is not due to measurement noise. Furthermore, similar trends can be observed in

both the good and poor recovery groups (Fig. 4D), suggesting that variation in independent fine finger control also occurred in patients with poor return of strength, albeit to a lesser extent.

Lesion size along CST was more strongly associated with control than strength.

To further investigate the underlying neural substrates for strength and fine finger control, we correlated the extent of motor-cortical gray matter lesions and the extent of the subcortical white-matter lesions with Strength and Individuation Indices. Because direct cortico-spinal projections to ventral horn neurons mostly arise from the anterior bank of the precentral gyrus/central sulcus (Rathelot and Strick, 2009, 2006), we predicted that lesions to this area would limit mostly the degree to which individuation can recover. In contrast, lesions in the subcortical white matter (including corona radiata, internal capsule, and cerebral peduncle) should disrupt both corticospinal and corticoreticular projections and should therefore impair and delay the recovery of both strength and individuation.

Indeed, for the precentral ROI (Fig 5B, see methods), the percentage of volume lesioned correlated significantly with the Individuation Index for all time points after W1 (W1: $r = -0.17$, $p = 0.31$; W4: $r = -0.46$, $p = 0.005$; W12: $r = -0.48$, $p = 0.003$; W24: $r = -0.59$, $p = 0.0002$; W52: $r = -0.60$, $p = 0.0007$; overall: $r = -0.43$, $p = 4.02 \times 10^{-9}$). The correlation with the strength index was generally weaker (W1: $r = -0.25$, $p = 0.14$; W4: $r = -0.29$, $p = 0.089$; W12: $r = -0.17$, $p = 0.31$; W24: $r = -0.36$, $p = 0.033$; W52: $r = -0.36$, $p = 0.059$; overall: $r = -0.24$, $p = 0.002$). Importantly, the lesion extent in the precentral

cortical gray matter was more strongly correlated with Individuation Index than with the Strength Index (Fig 5C, $z = 3.65$, $p = 0.0001$, (Steiger, 1980)).

In contrast, for our combined subcortical white-matter ROI (Fig 5C), the lesion volume vs. behavior impairment correlations were overall somewhat weaker, but still significant (Strength: $r = -0.18$, $p = 0.023$; Individuation: $r = -0.24$, $p = 0.002$), and there was no significant difference between strength and individuation (Fig. 5C, $z = 1.12$, $p = 0.13$).

Insert Figure 5

Discussion

We sought to track recovery of two independent behavioral components of hand function, strength and fine finger control, after stroke in a large-scale longitudinal study. Acute stroke patients were tested at five time points over a one-year period, using a novel device and paradigm that separately measures strength and individuation ability and crucially controls for any obligatory relationship between them. This approach allowed us to determine whether there is any systematic relationship between recovery of these two components, which would provide insight into the nature of the neural substrate underlying their recovery.

Relationship to extant clinical test

Traditional clinical scales are either impairment measures, such as the Fugl-Meyer scale, or activity measures, such as the ARAT, with the latter also likely reflecting the contribution of compensatory strategies (Kitago et al., 2013). Both types of scale, however, have in common that they depend on a mixture of strength and control. Consistent with this assumption, we found that FMA and ARAT were correlated with both Strength and Individuation Indices. Importantly, the Strength and Individuation indices were, despite excellent reliabilities, less correlated with each other than the two clinical scales were with each other. This supports the notion that strength and control make independent contributions to standard clinical recovery scales.

Recovery Time Course

The first finding was that for both strength and control, most recovery occurred over the first 3 months after stroke. This predominantly early recovery is consistent with what has been found in numerous other longitudinal studies using clinical scales of both impairment and function (e.g. Duncan et al., 1992; Jørgensen et al., 1995; Krakauer et al., 2012; Nakayama et al., 1994). The similarity between time courses for strength and control does not necessarily imply that recovery of these two aspects of hand function is due to a single neural system. It remains possible that recovery of these two components occurs in parallel because of commonalities in basic tissue repair mechanisms post-ischemia but that they are nevertheless independent modules.

Our purer measures of strength and strength-independent control allowed us to perform a finer-grained characterization of recovery time course than is possible with standard clinical measures. It is important to emphasize that our task was specifically

designed to remove any obligatory relationship between strength and control. That is, theoretically patients could show perfect control of individual fingers, even with significant weakness (except for complete hemiplegia, in which case no individuation measure would be obtainable). Furthermore, the Individuation Index was just as reliable at low levels of maximal force, giving us confidence that we could quantify control ability even in very weak patients.

Applying the new task and its associated measures, we found a small but robust difference in the time course of recovery of strength compared to control: finger strength showed a faster rate of change compared to finger control over the first month, a dissociation that would not be detectable with the FMA for example. While statistically maybe not the strongest dissociation, the differential time courses already hint at the possibility that the neural substrates for strength and control may be distinct. We will return to this issue later in the discussion.

Ipsilateral deficit

Interestingly, there was a small impairment in strength but not control in the hand ipsilesional to the stroke. This finding confirms previous reports of deficits in the non-paretic hand using clinical scales, e.g. muscle weakness measured by myometers in Colebatch and Gandevia (1989), and dexterity measured by Nine Hole Peg Test (9HPT) in Noskin et al. (2008). Of note, our current results appears inconsistent with the Noskin et al. study, which reported impaired control but preserved strength in the non-paretic hand. In this earlier study, control was measured with the 9HPT, which requires visually guided control of the proximal limb as well as precision grip. It is therefore possible that

impaired 9HPT performance can be attributed to a wider range of motor planning and execution deficits that extend beyond CST function. Furthermore, in the Noskin et al study, strength was assessed using grip dynamometry, which predominantly probes the strength in extrinsic hand muscles, not in the intrinsic hand muscles, which were assessed here. As shown in the Supplemental Materials (Fig. S2), grip strength, and strength in the FDI, and FCR muscles, as assessed by Dynamometry, did not show significant differences to controls. Thus it is possible that the ipsilateral strength deficit shown in our task is mainly apparent in the intrinsic hand muscles and that strength-independent control is mediated predominantly by contralateral projections and/or subcortical systems that project bilaterally.

Two recovery systems

Our main question was to ask whether there is a causal relationship between strength and control at the level of recovering neural substrate, after the two variables have been experimentally uncoupled from any obligatory relationship. That is to say, although good individuation is theoretically possible even in the setting of marked weakness (and vice versa), the question is whether such patients actually exist.

Our data revealed a time-invariant non-linear relationship between strength and individuation in the paretic hand. This function has two distinct parts: finger individuation and strength were highly correlated below a strength threshold of ~60% of the non-paretic side; beyond this point, they were uncorrelated. This function maintained the same shape across all measurement time points. Recovery of hand function therefore can be characterized as a movement along this invariant function: patients with good

recovery traveled further along the function; patients with poor recovery lingered around the first part (the left side of Fig. 3B). The strong correlation between strength and control for severely impaired patients would suggest that one single system is responsible for recovery of both.

We found, however, two pieces of behavioral evidence that strength and individuation may rely on partly separate mechanisms of recovery. First, the correlation between the two aspects of hand function was absent for the subset of well-recovered patients – i.e. patients with a strength index above 60%. This breakdown of the correlation is not due to a ceiling effect on individuation – indeed when we picked a subset of patients above the inflection point for strength, they still showed a significant impairment in individuation.

Secondly, we found that patients differed consistently in the amount of individuation/control recovery, over and above what would be predicted by the time-invariant strength-individuation relationship. Analysis of the residuals around the mean invariant function revealed that their positioning relative to the mean recovery curve seemed to be decided early in the recovery process and then remained relatively stable at later time points. ----------

Insert Figure 6

Thus, we propose that recovery of strength and individuation relies on two separate modules. The first module would generate the main hand strength, but would also have some limited control capacities. The isolated contribution of this system would determine the lower bound of the data points in the strength-individuation plot (dashed

line in Fig. 6): If a patient regains some strength, he or she automatically regains a limited amount of control with it. However, the amount of individuation is limited and does not increase above a certain level. This would explain both the strong correlation between strength and control for the severely impaired patients, and the fact that we did not observe any patient that fell into the lower right corner of the strength-individuation space (good strength, but minimal control).

The second system would then add additional control capacities into this rudimentary individuation recovery (vertical arrows in Fig. 6). Patients with a strong contribution from this system may gain full recovery of individuation; patients with no or partial functioning of the system may recover completely in strength, but not in individuation. Importantly the major plastic changes in the biological system responsible for this additional control also occur early after stroke, with the relative position above or below the mean recovery function remaining relatively fixed subsequently (Fig. 3D)

Neural substrates for two recovery systems

Our lesion analysis corroborates the model of two recovery modules as suggested by the behavioral data. A wealth of evidence in humans and non-human primates implicates the CST in fine finger control, specially the monosynaptic cortico-motoneuronal connections originating from "new" M1 (Rathelot and Strick, 2009, 2006). Notably, these connections do not generate high levels of force but instead finely graded forces riding on top of larger forces (Maier et al., 1993). Consistent with this idea, lesions to the gray matter of the precentral gyrus, the main origin of cortico-spinal projections, correlated with impaired individuation recovery after 1 year. In contrast, a strong hand

Kommentiert [andreas.l7]: Reviewers may ask how many pure cortical lesions we had.

Kommentiert [JX8]: We originally planned to do this level of analysis, but turns out that there is not a clear distinction between cortical vs. sub-cortical, and mixed lesions. After discussions with Andreia, we then decided to move on to her measure of percentage volume affected. My analysis showed that precentral gyrus gray matter and white matter immediately beneath precentral gyrus showed very similar correlations to Strength and Individuation Indices.

grip may rely on other neural pathways, including the reticulospinal tract (RST) (Buford and Davidson, 2004), which can support strength and gross, proximal movements (Lemon, 2008; Porter and Lemon, 1993; Rathelot and Strick, 2009, 2006). Although the RS tract has been found to participate in hand function and may endow the system with a modicum of hand control, the functional range is limited and biased towards flexor muscles (Baker, 2011; Riddle et al., 2009)**.**

Even though the primary motor cortex also projects to the reticular formation (Catsman-Berrevoets and Kuypers, 1976; Jones and Wise, 1977), the origin of the cortico-reticular inputs is likely more diffuse (Keizer and Kuypers, 1989) and bi-laterally organized(Buford and Davidson, 2004; Sakai et al., 2009; Soteropoulos et al., 2012). This may explain why some patients recover hand strength completely, but are being left with a residual impairment in finger individuation. Lesions in the subcortical white matter likely disrupt both cortico-spinal and cortico-recticular projections equally , and therefore, are predictive of recovery in both strength and individuation to a similar degree.

Recovery after stroke may be the result of a dynamic interplay between the CST from M1 and the RST. In this scenario, the correlation between strength and control at low levels of strength may represent the state of both the residual CST and cortical projections to reticular nuclei in the brainstem. Recovery along the lower bound of the invariant function would represent facilitation of the intact RST. Those patients with more recovery of the CST would consistently ride above the RST function. The correlation of Individuation Index with cortical level lesion sizes suggests that this additional component is mainly driven cortical plasticity in the precentral gyrus.

Conclusions

Here we found that hand function after stroke could be partitioned into strength and strength-independent control. Most recovery of both these components occurred in the first months after stroke. At any time point after stroke, strength and strength-independent control were related by an invariant curvilinear function. This function has characteristics consistent with the properties of the reticulospinal tract: strength and some degree of control are correlated up to a certain strength level and then control saturates. Some subjects showed additional improvement in individuation riding on top of the main recovery function, which is likely attributable to a concomitant contribution by the residual CST, more specifically cortical-level reorganization. Thus recovery of the hand can be attributed to at least two processes that show most change in the first month after stroke.

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Supplemental Materials

Patient characteristics

Patient	Age at stroke	Gender	Paretic Side	Initial impairment (FMA)	Initial MoCA
1	57	M	R	48	27
2	24	M	L	35	23
3	67	F	R	16	23
4	74	F	R	39	17
5	61	F	L	48	26
6	59	F	R	60	28
7	57	M	R	54	27
8	66	M	L	65	25
9	42	F	R	5	18
10	65	M	L	30	25
11	66	F	L	60	19
12	51	M	L	34	25
13	63	F	L	57	26
14	55	M	L	0	26
15	56	M	L	38	25
16	56	M	L	64	24
17	64	F	R	20	16
18	60	F	R	55	21
19	64	M	L	63	25
20	25	F	L	42	29
21	39	F	L	47	20
22	46	M	L	9	27
23	53	F	L	4	29
24	66	M	L	59	24
25	71	M	L	4	26
26	52	M	L	53	24
27	46	M	R	4	21
28	46	M	L	49	30
29	71	M	L	6	24
30	47	M	R	57	10
31	45	M	L	8	27
32	55	F	L	19	25
33	68	F	L	61	NaN
34	65	M	L	32	28
35	51	F	L	63	26
36	42	M	R	54	25
37	58	M	L	4	24

38	41	F	L	4	23
39	35	M	L	4	29
40	68	M	L	52	27
41	76	M	L	53	18
42	86	M	L	54	20
43	48	M	L	16	25
44	74	M	R	5	25
45	80	F	R	9	24
46	64	F	L	58	19
47	22	M	R	63	27
48	88	F	R	55	28
49	22	M	R	63	27
50	87	F	R	50	28
51	84	M	R	30	26
52	53	M	R	30	29
53	54	M	L	59	21
54	58	M	R	61	23

Table S1. *Patient characteristics: age* (*years*)*, sex, paretic side, initial FMA* (*Fugl-Meyer arm score, maximum 66*)*, initial MoCA* (*Montreal Cognitive Assessment, maximum 30*)*.*

Lesion distribution

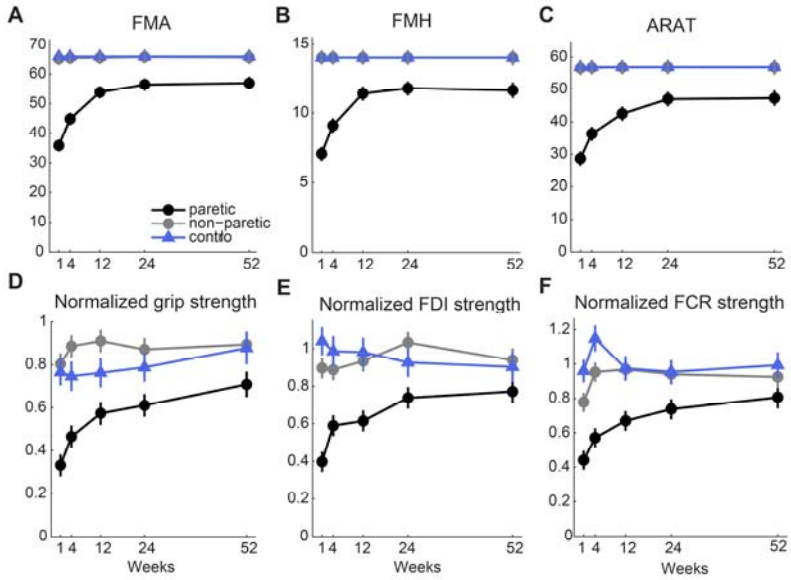
To define boundary(s) of acute stroke lesion(s) of each participant, a threshold of >30% intensity increase from the unaffected area in the diffusion-weighted image (DWI) was applied. A neuroradiologist (AVF), blind to the patients' clinical information, manually modified the boundary to avoid false-positive and false-negative areas on RoiEditor (www.MRIstudio.org). Each brain was then mapped to a single subject adult template, the JHU-MNI atlas (Mori et al., 2008), previously segmented in more than 200 regions of interest, using affine transformation followed by dual channel (b0 and FA) large deformation diffeomorphic metric mapping (LDDMM) (Ceritoglu et al., 2009). For the brain mapping, we first used "artificial" images, in which the stroke area was masked

out and substituted by the normal images from the contralateral hemisphere. This helped to minimize inaccuracies caused by the focal changes in intensity due to the stroke. The parcellation map template was then applied to each subject's deformation fields. The percentage volume affected by acute stroke within the following structures was calculated: corticospinal tract (CST) at pyramids level, posterior limb of internal capsule, superior corona radiata, cerebral peduncle, pre-central gyrus, white matter beneath the pre-central gyrus. The percentage of the entire CST affected by the stroke in each patient was also quantified by applying the deformation fields to a probabilistic map of CST (cmrm.med.jhmi.edu) (Zhang et al., 2010), thresholding to 70%.

To quantify the pre-central cortex affect by stroke, a slightly modified approach, optimizing for cortical segmentation, was used. Brain mapping and parcellation were based on high-resolution T1-WI (MPRAGE) and the combination of LDDMM and Multi-Atlas Label Fusion algorithm - MALF (https://braingps.anatomyworks.org) (Tang et al., 2015). Using a mutual-information based algorithm, the stroke mask was brought to the MPRAGE by co-registering it to the DWI, in which the stroke was defined. Although the acute MPRAGE intensity was not affected by the stroke in most of the cases, possible focal changes that could affect the diffeomorfic transformation were corrected by creating "artificial" images used just for mapping, as described above.

Recovery measured in classical clinical assessment

In addition to the Strength and Individuation Indices, we also compared the recovery trajectories for the hand function assessed by classical clinical measures, such as Fugl-Meyer, ARAT, and strength as measured by Dynamometry.



869

870 ***Figure S1.*** *Recovery curves for clinical assessment Fugl-Meyer Arm (**A**), Fugl-Meyer*

871 *Hand (**B**), ARAT (**C**), and hand strength measures by Dynamometry on hand grip (**D**),*

872 *FDI (**E**), and FCR (**F**).*

873

874 ***Two-segment piecewise linear regression for modeling time-invariant function***

875 For the two-segment piecewise linear function, let x be the predictor with two

876 segments separated by a constant breakpoint c, $x_1 \leq c$ and $x_2 \geq c$. The linear functions for

877 each segment are

878
$$y_{1i} = b_{10} + b_{11}x_{1i} + e_{1i}$$
$$y_{2i} = b_{20} + b_{21}x_{2i} + e_{2i}$$

879 The two pieces can be joint at the breakpoint constant c by setting $y_{1i} = y_{2i}$, yielding

880
$$b_{20} = b_{10} + (b_{11} - b_{21})c$$
$$y_{2i} = b_{10} + (b_{11} - b_{21})c + b_{21}x_{2i} + e_{2i}$$

881 Putting the two pieces together, we have the full model

882 $$y_i = a + b_1 x_i \cdot I(x_i \le c) + \left[(b_1 - b_2)c + b_2 x_i \right] \cdot I(x_i \ge c) + e_i$$

883 where $I(\cdot)$ is an indicator variable, coded as 1's or 0's to indicate the condition satisfied.

884

	Strength Index	Individuation Index	FMA	ARAT
Strength Index		0.73	0.77	0.76
Individuation Index			0.70	0.75
FMA				0.91

Table 1. *Correlation between MVC, Individuation Index, FMA* (*Fugl-Meyer arm score, maximum 66*), *and ARAT* (*Action Reach Arm Test, maximum 57*). *All four measures are highly correlated; however Strength and Individuation Index show the weakest correlation, whereas FMA and ARAT show the strongest correlation.*

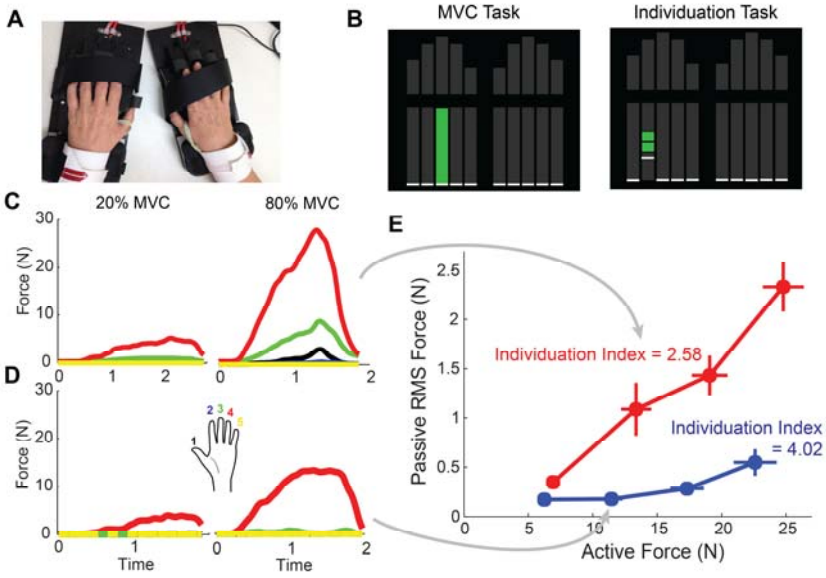
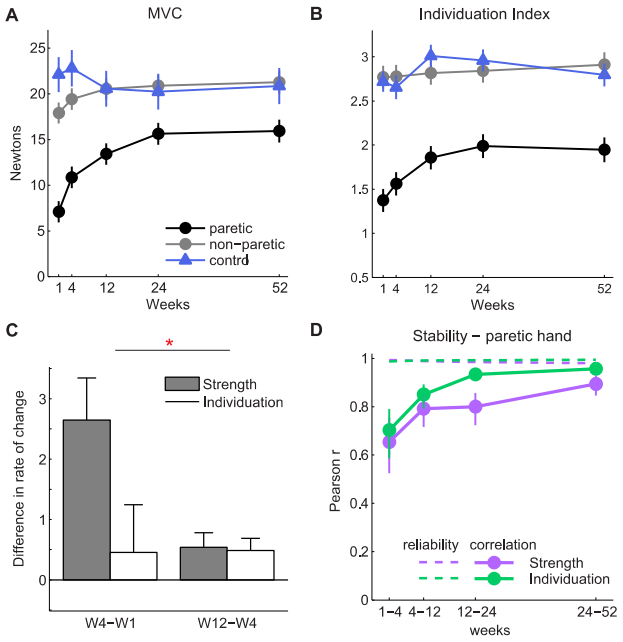


Figure 1. *Strength and Individuation task. (**A**) Ergonomic hand device. A participant's fingers are securely placed on the keys using Velcro straps. (**B**) Visual stimuli showing the instructional stimulus, which indicates both which finger to press (left middle finger) and how much force to produce (height of the green bar). (**C**, **D**) Example trials from two healthy control participants during the individuation task. Four trials are shown, one at 20% and one at 80% of MVC for each time point. In this case the fourth finger (red) was the active finger. Note the higher level of enslaving of the passive fingers for higher active force level. (**E**) Mean deviation from baseline in the passive fingers plotted against the force generated by the active finger for (C) and (D). Increased enslaving with increasing active force levels is clearly visible. The Individuation Index is the -log(slope) for the regression line between active force and passive mean deviation.*

Kommentiert [andreas.l9]: Average of four trials?

Kommentiert [JX10]: No. Each trace represent the real-time response within one trial, so the four sub-plots showed four trials.



905

906 ***Figure 2.*** *Temporal profiles of recovery for strength and individuation.* (***A-B***) *Group*

907 *recovery curves for the Strength and Individuation Indices for patients and controls.* (***C***)

908 *Rate of change in Z-normalized Strength and Individuation Indices during the first two*

909 *time segments showed significant interaction, indicating faster initial improvement of*

910 *strength;* (***D***) *Week-to-week correlations between adjacent time points for the Strength*

911 *and Individuation Indices. Dashed lines are stabilities across the same time points for the*

912 *correlations.*

913

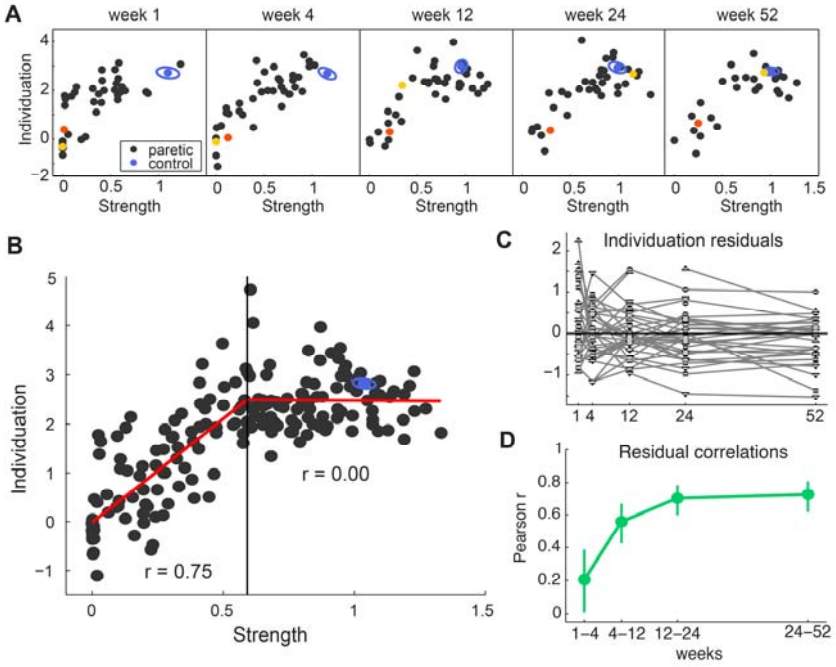


Figure 3. *Time-invariant impairment function relating strength and control. (**A**) Scatter plots for Individuation Index against Strength Index at each time point. Each black dot is one patient's data; blue dots and ellipses are the means and standard errors for controls at each time point. Two patients' data are highlighted: one with good recovery (yellow dot) and one with poor recovery (red dot). (**B**) Scatter plot with data from all time points supper imposed with the best fitting two-segment piecewise linear function with one inflection point at Strength Index = 0.592. (**C**) Line plot of residuals from each week subtracting out the mean impairment function, showing the remaining structure for Individuation Index on top of the mean function. (**D**) Correlations of residuals in (C) across adjacent time points increased over time.*

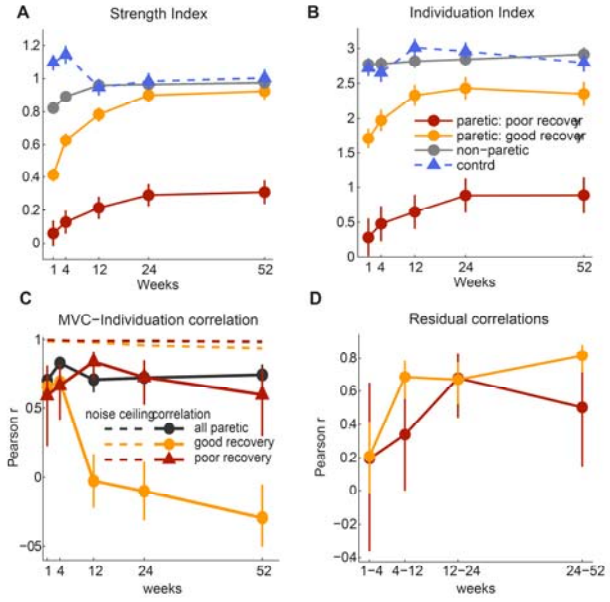
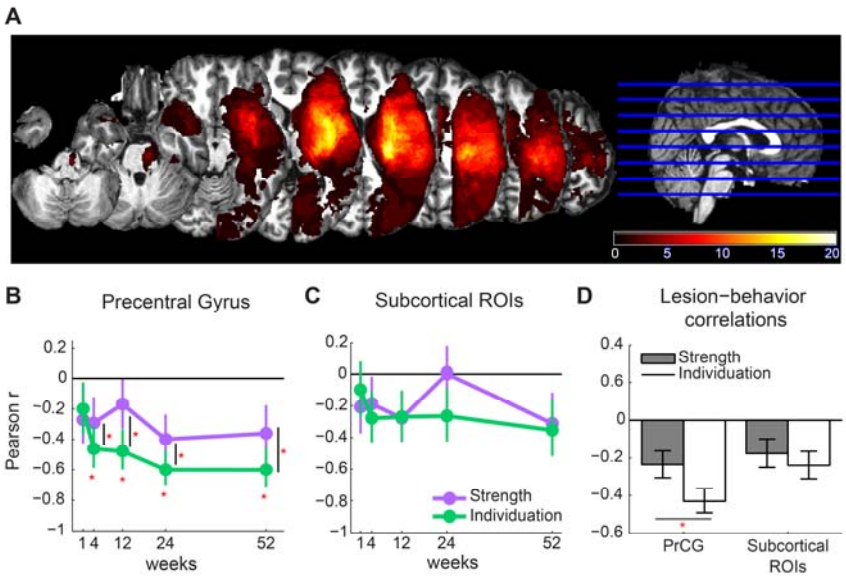


Figure 4. *Analysis of the paretic hand data stratified to good vs. poor recovery by final strength level (mean(W24, 52)). Cut-off value for the two groups is the inflection point in the best fitting piecewise linear function to the entire data set. (**A-B**) Time course of recovery for Strength and Individuation Indices; (**C**) Correlation between Strength and Individuation Indices across time; (**D**) correlation of residuals after subtracting the mean impairment function.*



932

933 ***Figure 5.*** *Lesion distribution and correlation with behavior.* ***(A)*** *Averaged lesion*

934 *distribution mapped to JHU-MNI space (see Supplemental Materials), with lesion flipped*

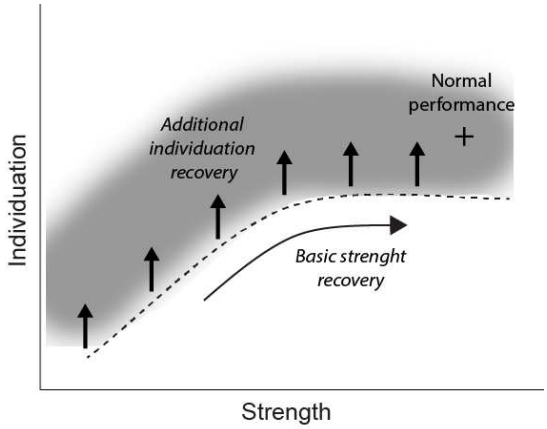
935 *to one hemisphere. Color bar indicates patient count.* ***(B-D)*** *Correlation between lesion*

936 *size and behavior measures of Strength and Individuation Indices for cortical gray matter*

937 *within precential gyrus* ***(B)*** *vs. subcortical white matter ROI's* ***(C)*** *for each time point,*

938 *and entire data across all time points* ***(D)****. Error base are standard error for correlations.*

939



940

941 ***Figure 6.*** *A schematic diagram of the hypothesis of two recovery systems. The first*
942 *system (basic strength recovery) underlies strength recovery and a restricted amount of*
943 *individuation recovery. This system therefore defines the lower bound (dashed line) of the*
944 *space occupied by recovery patients (gray clound). A second system (additional*
945 *inidividuation recovery) adds further individuation abilities on top of the basic strength*
946 *recovery.*